STATUS OF CLAIMS:

Claims 1-16, 18-23, 29-31, 33-44, 46, 50, 52 and 53 are presently pending.

Claims 52 and 53 have been amended as requested by the Examiner.

REMARKS:

Rejection of Claims 1-16, 18-23, 29-31, 33-44, 46, 50, 52 and 53--35 U.S.C. 103(a)

Claims 1-16, 18-23, 29-31, 33-44, 46, 50, 52 and 53 continue to be rejected under 35 U.S.C. 103(a) as obvious over Song et al. in view of Hedley et al. and Fattal et al. Applicants respectfully traverse this rejection and its supporting remarks.

In order to establish a *prima facie* case of obviousness under 35 U.S.C. 103, (a) there must be some suggestion or motivation to modify/combine the references of record, and (b) there must be a reasonable expectation of success. See MPEP §2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *Id.* The mere fact that references *can* be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination or modification. MPEP 2143.01 (emphasis added) (citing *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)).

Claim 1, the only independent claim presently pending, reads as follows:

> 1. A method of transfecting dendritic cells comprising:
> providing dendritic cells;
> providing a transfection agent comprising polynucleotide adsorbed on surfaces of microparticles, said transfection agent being formed by a process that comprises: (a) providing microparticles comprising a biodegradable polymer and a cationic detergent, and (b) exposing said microparticles to said polynucleotide, said polynucleotide encoding an antigen associated with a virus, a bacterium, a parasite, a fungus or a tumor; and
> incubating the dendritic cells and the transfection agent *ex vivo* for a time sufficient to transfect the dendritic cells with the polynucleotide, thereby leading to the expression of said antigen.

Claim 1 is unobvious over Song et al. in view of Hedley et al. and Fattal et al.

According to the Office Action, Song et al. teaches methods of transfecting dendritic cells *ex vivo* or *in vitro* with a gene delivery vehicle comprising DNA encoding an antigen, such as a tumor antigen or HIV antigen, and use of the transfected dendritic cells to induce an immune response against the expressed antigen *in vivo*. Regarding gene delivery vehicles taught by Song et al., the Office Action agues that Song et al. teaches that for *ex vivo/in vitro* transfection of dendritic cells, both non-viral and viral gene delivery vehicles can be used, including the use of expression vectors complexed with polycations or lipids or encapsulated in liposomes. The Office Action concludes that Song et al. teaches that numerous gene delivery vehicles can be successfully utilized to transfect dendritic cells including the use of plasmid/liposomes, and plasmid combined with cationic condensing agents.

Even assuming that Song et al. does disclose various non-viral and viral gene delivery vehicles for both *ex vivo* and *in vivo* transfection of dendritic cells, in view of Song et al.'s preference for direct injection of recombinant retroviruses (see, e.g., Song et al., page 27, lines 25-27), it is respectfully submitted that one of ordinary skill in the art at the time of the invention, upon considering Song et al., *as a whole*, and in combination with Hedley et al. and Fattal et al. (each discussed below), would have been motivated to use recombinant retroviruses for *in vivo* polynucleotide-based transfection of dendritic cells.

In view of the above, the Office is reminded that "[i]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Wesslau*, 353 F.2d 238, 241, 147 U.S.P.Q. 391, 393 (C.C.P.A. 1965); *see also Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 448-49, 230 U.S.P.Q. 416, 420 (Fed. Cir. 1986) (holding that district court, by failing to consider a prior art reference in its entirety, ignored portions of the reference that led away from obviousness).

Moreover, among the non-viral techniques taught by Song et al., none uses a transfection agent comprising a polynucleotide adsorbed to microparticles as claimed.

Recognizing this, the Office Action turns first to Hedley et al., arguing that this reference is cited for its teachings regarding the use of microspheres comprising biodegradable polymers and DNA plasmids to introduce and express antigens encoded by the plasmids in antigen presenting cells such as macrophages and dendritic cells, both *in vitro* and *in vivo*, for the purpose of stimulating antigen specific immune responses. It is further argued that Hedley et al. provides motivation for introducing plasmid DNA encoding an antigen to antigen presenting cells such as macrophages and dendritic cells using biodegradable microspheres by teaching that DNA combined with biodegradable microparticles is efficiently phagocytosed by APCs and is an effective means for introducing nucleic acids into these cells. The Office Action further argues that Hedley et al. recognizes that dendritic cells are a "legitimate target" for microparticle transfection when they state that the point of introduction of plasmid/microparticles to skin is the transfection of dendritic cells.

Applicant respectfully disagrees with this characterization of Hedley et al.

First of all, it is respectfully submitted that, upon reviewing this reference as a whole, in combination with Song et al. and Fattal et al. (Fattal et al. is discussed below), a person of ordinary skill in the art would have been motivated to use *in vivo*, rather than *ex vivo,* transfection techniques, particularly with respect to dendritic cells.

For example, Hedley et al. teaches at col. 8, lines 20-34 that microparticles can be delivered in the following ways: (a) directly into the bloodstream (i.e., by intravenous or intra-arterial injection or infusion), (b) by subcutaneous injection, (c) intradermally, (d) via the gastrointestinal tract, or (e) into the lung. See. Each of these techniques is an *in vivo* technique.

The only reference to dendritic cells in all of Hedley et al. is in conjunction with technique (c) above, specifically, the *in vivo, intradermal* introduction of microparticles "to the APCs of the skin, such as dendritic cells and Langerhans cells". See col. 8, lines 20-34. It is respectfully submitted that Hedley et al.'s statement that microparticles can be "introduced" intradermally to dendritic cells that are inherently present in the skin would hardly provide motivation to one of ordinary skill in the art to pursue the *ex vivo* transfection of dendritic cells.

Because Hedley et al. describes the *in vitro* phagocytosis of DNA-containing microparticles in Example 2, much is made in the Office Action concerning the fact that dendritic cells and macrophages are both antigen presenting cells. However, this *in vitro* example is only a prelude to the *in vivo* studies that follow in Examples 3 *et seq.*, which as indicated above, is the goal of Hedley et al. Moreover, one of ordinary skill in the art would readily recognize that among antigen presenting cells, macrophages and dendritic cells are different in many characteristics, including the relative ease of transfection using non-viral means.

In view of the above, it is respectfully submitted that one of ordinary skill in the art, upon reviewing Song et al. and Hedley et al., would not have been motivated to pursue the *ex vivo* transfection of dendritic cells using polymer microparticles, even microparticles containing an *encapsulated* polynucleotide as described in Hedley et al.

The teachings of Fattal et al. do not make up for these deficiencies.

In addition, the Examiner is aware that Song et al. and Hedley et al. neither teach nor suggest the use of microparticles, which comprise a biodegradable polymer and a cationic detergent, and which have polynucleotide adsorbed on their surfaces, and turns to Fattal et al. to provide this feature of the invention.

However, one of ordinary skill in the art upon reviewing Fattal et al. would not have been motivated to use the nanoparticle *oligonucleotide* delivery vehicle of Fattal et al. in conjunction with a *polynucleotide that expresses antigen* as claimed.

For example, Fattal et al. reports that a 15-mer oligonucleotide adsorbed onto polyalkylcyanoacrylate nanoparticles is internalized in U-937 cells, a human macrophage-like cell line, by an "endocytotic/phagocytotic" process and that the oligomer remains intact for several hours after uptake. Of course, oligonucleotides *per se* do not function in the same manner as a plasmid which encodes and expresses an antigen, and it is respectfully submitted that the mere fact that a 15-mer oligonucleotide remains intact in the U-937 cells following adsorption to the surface of nanoparticles would *not* lead one of ordinary skill in the art to expect that that the oligonucleotide would have activity within the cell, even antisense activity, which is the goal of Fattal et al..

Moreover, this finding certainly would not have lead to the expectation that plasmid DNA encoding an antigen would efficiently be transcribed, translated, and processed.

In this regard, Fattal et al. teaches at page 140 that "[a]bout 20% of the oligonucleotide given *free or delivered by PIHCA nanoparticles* were found in the nuclear fraction." (Emphasis added.) Upon reading this, one of ordinary skill in the art upon would have had no motivation whatsoever to go to the trouble of adsorbing plasmid DNA to particles, because this effort would *not* have been expected to enhance the delivery of the plasmid DNA to the nucleus (i.e., the location where expression take place in the cell), relative to the administration of free DNA.

Furthermore, it is respectfully submitted that one of ordinary skill in the art would not have been motivated to draw inferences between the teachings of the Song et al., Hedley et al. and Fattal et al., because these references each describes a different approach for DNA uptake. For example, Song et al. describes the use of DNA complexed with polycations or lipids or encapsulated in liposomes, but does not teach DNA encapsulated within or adsorbed to microparticles. Hedley et al. describes encapsulated DNA within microparticles, while Fattal et al. teaches DNA adsorbed to nanoparticles. With respect to the latter two techniques, at the time of the present invention, DNA adsorption and DNA encapsulation were understood by those of ordinary skill in the art to constitute separate and distinct delivery approaches, with some favoring encapsulation based on the notion that the DNA would be protected from the destructive elements (e.g., nucleases) in the biological milieu, and others favoring adsorption based on the notion that the DNA would be protected from destructive force elements (e.g., high shear stresses) within the processing environment.

Regarding encapsulation vs. adsorption, the Office Action states as follows at pp.7-8: "The applicant further argues that the claims as amended now read on microparticles where the nucleic acid is adsorbed onto the surface and that Hedley et al. teaches that nucleic acid is encapsulated within the microparticle. In response, the claims as amended still encompass microparticles with encapsulated nucleic acid; see in particular, claims 46 and 50 which specifically recite wherein a portion of the polynucleotide is entrapped within said microparticles."

First, Applicant is presently arguing the patentability of independent claim 1, the only independent claim presently pending. Among the features of this claim is a transfection agent comprising polynucleotide adsorbed on surfaces of microparticles, which is formed by a process that comprises: (a) providing microparticles comprising a biodegradable polymer and a cationic detergent, and (b) exposing the microparticles to said polynucleotide, the polynucleotide encoding an antigen associated with a virus, a bacterium, a parasite, a fungus or a tumor.

Of course, being generic, claim 1 *encompasses* many other features, including particles which further comprise entrapped polynucleotide as set forth in dependent claims 46 and 50. However, this fact is irrelevant to the feature of claim 1 that is at issue, i.e., a transfection agent comprising polynucleotide adsorbed onto surfaces of microparticles that comprise a biodegradable polymer and a cationic detergent. In this regard, "the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and *with no knowledge of the claimed invention*, would select the elements from the cited prior art references for combination in the manner claimed." *In re Rouffet*, 149 F.3d 1350, 47 U.S.P.Q.2d 1453, 1458 (Fed. Cir. 1998).

For at least the above reasons, it is respectfully submitted that one of ordinary skill in the art would not have been motivated to perform the method set forth in claim 1 in view of the teachings of Song et al., Hedley et al. and Fattal et al.

For at least the above reasons, it is respectfully submitted that a *prima facie* case of obviousness has not been established with respect to the presently pending claim 1.

Claims 2-16, 18-23, 29-31, 33-44, 46, 50, 52 and 53 depend from claim 1 and are therefore patentable for at least the same reasons as is claim 1.

Reconsideration and withdrawal of the outstanding rejection under 35 U.S.C. §103(a) are therefore respectfully requested.

Objection to Claims 52-53

Claims 52-53 are objected to under 37 CFR 1.75(c) as allegedly being in improper form because a multiple dependent claim must refer to the parent claims in the

alternative. This objection is believed to be moot in view of the above amendments to claims 52-53.

CONCLUSION

All pending claims are in condition for allowance, notification of which is earnestly solicited. The Examiner is invited to telephone the Applicant's attorney at (703) 433-0510 to resolve any outstanding issues in this case.

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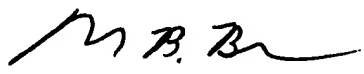
Respectfully submitted,



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